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# The Role of RNF145 in Renal Epithelial Cell Metabolism: Lipid and Oxygen Sensing Mechanisms

In diabetic patients, factors such as dyslipidemia and hypoxia drive kidney damage. Our previous research using induced renal epithelial cells (iRECs) and a pharmacological mouse model of diabetes combined with a high-fat diet demonstrated that palmitic acid (PA), a saturated fatty acid induces ER stress and lipotoxicity in proximal tubular cells in vitro and in vivo, whereas monounsaturated oleic acid (OA) does not. Moreover, in a transcriptomic approach to assess genes differentially regulated by lipid saturation we uncovered the ring-finger protein 145 (RNF145), an E3-ubiquitin ligase that targets adiponectin receptor 2 (ADIPOR2) a protein with antidiabetic effects.

Our major aim is to uncover the role of RNF145 in PA-mediated toxicity and in hypoxia adaptation as well as to identify the metabolic cues regulating RNF145 and ADIPOR2 levels. To this end Rnf145, knockout (KO) iRECs were analyzed for cell viability, protein, and mRNA expression and bioenergetic profiling under both lipotoxic and hypoxic conditions.

Depletion of Rnf145 partially protected iRECs against PA-mediated lipotoxicity by upregulating ADIPOR2, reducing ER stress and cell death. Furthermore, both chemical and physiological hypoxia downregulates RNF145 levels, leading to the stabilization of ADIPOR2. In parallel, RNF145 deficiency enhanced cell survival in hypoxia. Potentially due to the normoxic upregulation of genes typically induced by hypoxia. In addition, RNF145 KO cells showed higher basal mitochondrial respiration and reduced glycolysis.

Collectively, our findings suggest that RNF145 serves as a key regulator of lipid homeostasis and oxygen sensing shaping the metabolic profile of renal epithelial cells, highlighting its potential as a Reno-protective target in both lipid-mediated toxicity and the adaptation to hypoxia.

## Research type

Basic research

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